

Privileged and Confidential

May 10, 1994

Memorandum to Messrs. Bushong and WinokurRe: IARC and Quantitative Estimation

We were asked at Friday's meeting to summarize what we know of an IARC paper dated March 1994 making recommendations regarding the agency's possible use of quantitative estimation and prediction ("QEP") methods with respect to cancer risks. This provides such a summary. I am sending it only to you, and leave any further distribution to your judgment.

1. Background. We understand that virtually every IARC working group has included members who want to use QEP to add specificity and punch to IARC's bland qualitative classification system. Our consultants believe that this probably explains the agency's decision to convene a working group to consider the issue. We are, however, continuing to explore the question, and it is by no means impossible that the report resulted from U.S. pressures.

2. The working group. A group of 23 was involved, including 10 from the U.S. The Americans included a representative of NCI, one from EPA, one from NIOSH, two from the National Institute of Environmental Health Sciences, and one from ILHI. There were 6 from the EU (including one from the Commission's environmental DG), plus one each from Sweden and Norway. The Norwegian is the country's most vehement anti-smoker, and a fervid user of quantitative estimates. There were two each from Australia and Canada, plus one Swiss. The Swiss was from WHO in Geneva. The chairman was one of the Australians, from the University of Adelaide. Putting aside ILHI, there was no one identifiable as from industry. There appear to have been no observers. Three others, all Americans, were invited but could not attend. They were all government-related, including another EPA representative. The secretariat list includes Boffetta, Tomatis and Vainio, among others.

3. IARC's use of QEP. The report begins with a description of IARC's general policy of avoiding QEP in the monograph series, which it largely attributes to uncertainties about QEP's reliability when the series was initiated. It notes that QEP involves a "a large judgmental component" which may significantly influence its results. The report observes, however, that IARC has contributed to QEP estimates outside the monograph series

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involve "uncertainty," encourages the identification of confounders and modifying factors, and states that physiologically-based pharmacokinetic modeling is "potentially" of great value in QEP. It states that accurate exposure data are "essential" for reliable QEP estimates, and that extrapolations between populations must be made with "caution."

6. Recommendations. The report recommends that the monograph series should not be altered, and that QEP should not be used in them, but urges the inclusion of more and better quantitative estimates and data. In other words, the monographs should do a better job of facilitating separate QEP estimates and predictions. Moreover, the report recommends that IARC should prepare QEP estimates for selected carcinogens about which extensive data are available, and publish them separately from the monograph series. No specific carcinogens were suggested for this purpose. It also recommends efforts to develop improved exposure measurements, including the use of biological markers, and the conduct of studies specifically designed to examine risks at low exposure levels. The report also encourages IARC to conduct scientific meetings and training programs regarding the proper use of QEP methods.

7. Conclusions. Unsurprisingly, the essence of the report is an encouragement to IARC to use QEP more widely and forcefully, and to facilitate its use by WHO and regulators. Given the frailties of the process, and its susceptibility to abuse, this is not good news. On the other hand, the report at least catalogs the weaknesses of QEP and encourages a greater and more consistent degree of professionalism and responsibility. Many of the warnings and caveats identified by the report (although not always highlighted) are precisely those we have long suggested.

We assume that the report will in due course be published (there is characteristically a delay of several months to a year), and, once it is, the report may be a useful source of evidence regarding the weaknesses and hazards of QEP.

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